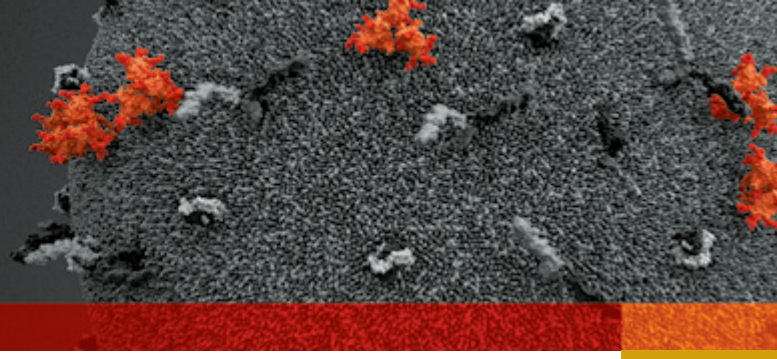

Recent scientific advances resulting from NIH-funded research represent a turning point for AIDS research. New avenues for discovery have been identified, providing possibilities for the development of new strategies to prevent, treat, and potentially cure HIV. The NIH is leading global research efforts to capitalize on those advances, move science forward, and begin to turn the tide against this pandemic.

While the NIH investment in AIDS research has produced groundbreaking scientific advances, many serious challenges lie ahead. There is little doubt that, despite our progress to date, the AIDS pandemic will continue to affect virtually every sector of society in nearly every nation in the world for decades to come. In light of this reality, the U.S. national commitment to AIDS research remains strong. The NIH will continue to build on this important moment in science and to support critical research to find new tools to turn the tide in the fight against AIDS—so that we can all once again live in a world without AIDS.

30 Years of Extraordinary NIH AIDS Research Accomplishments

- In the three decades since AIDS was first reported, the NIH has been the global leader in research to understand, prevent, diagnose, and treat HIV and its many related conditions. From the development of the first blood test for HIV infection and the discovery and clinical testing of the first effective therapies, through today's research to determine whether a vaccine, microbicide, or eventual cure for AIDS will one day be possible, NIH research has transformed HIV from a mysterious and uniformly fatal infection into one that can be accurately diagnosed and effectively managed with appropriate treatment. A recent study estimated that 14.4 million life-years have been gained since 1995 by the use of AIDS therapies developed as a result of NIH-funded research.[1] NIH research has resulted in landmark advances that have led to:
- Co-discovery of HIV, the virus that causes AIDS;
- Development of the first blood test for the disease, which allowed diagnosis of infection and ensured the safety of the blood supply;
- The critical discovery of key targets that enabled the development of effective antiretroviral therapies and multidrug regimens for the treatment of AIDS;
- The development of treatments for many HIV-associated coinfections, comorbidities, malignancies, and clinical manifestations;
- Groundbreaking strategies for the prevention of mother-to-child transmission (PMTCT), which have resulted in dramatic decreases in perinatal HIV in the United States, where now fewer than 200 babies a year are born with HIV infection;
- Demonstration of efficacy of medical male circumcision in significantly reducing the risk of HIV acquisition;
- Demonstration of the first proof-of-concept that a vaccine can prevent HIV infection, and discovery of two potent human antibodies that can stop more than 90 percent of known global HIV strains from infecting human cells in the laboratory;
- Demonstration of the first proof-of-concept that a microbicide gel can prevent HIV transmission;

[1] *Sexually Transmitted Infections*. 2010 Dec; 86 Suppl 2:ii67–71.

- Demonstration that the use of antiretroviral therapy (ART) by infected individuals can reduce HIV transmission to an uninfected partner dramatically;
- Demonstration of the feasibility of pre-exposure prophylaxis (PrEP), the use of antiretroviral (ARV) treatment regimens by uninfected individuals to reduce their risk of HIV acquisition;
- Discovery that genetic variants may play a role in enabling some individuals, known as "elite controllers," to control HIV infection without therapy;
- Critical basic science discoveries that continue to provide the foundation for novel research; and
- Advances in basic and treatment research aimed at eliminating viral reservoirs in the body, which, for the first time, is leading scientists to design and conduct research aimed at a cure for HIV/AIDS.

Today, NIH research provides the scientific basis and the necessary tools to facilitate the implementation of the President's National HIV/AIDS Strategy (*http://www.whitehouse.gov/administration/eop/onap/nhas)*.

The goals of the Strategy are to:

- Reduce HIV incidence
- Increase access to care and optimize health outcomes
- Reduce HIV-related health disparities.

Recent Scientific Advances and Opportunities

The NIH's ongoing investments in AIDS research have produced critical advances in our understanding of HIV and in the development and improvement of strategies to prevent and treat HIV and AIDS. Recent progress in basic, prevention, treatment, and implementation research provides the groundwork for further scientific investigation and the building blocks for new approaches to reduce, and ultimately end, this pandemic. Among these are:

Advances in Basic Science

- **Genetics/genomics research:** The National Institute of Allergy and Infectious Diseases (NIAID) scientists have demonstrated why certain immune cells chronically exposed to HIV shut down, and how they can be reactivated. The investigators used small interfering RNAs (siRNAs), which acted at the genetic level to prevent exhausted B cells from replenishing inhibitory receptors. The new siRNA-based approach may hold promise for scientists seeking to develop therapies to improve the human antibody response against HIV and other pathogens by altering the expression of specific B-cell genes.[2]
- **Characteristics of HIV early in transmission:** NIAID research findings help to explain genetic differences that can distinguish some early-transmitting viruses found in an infected individual within the first month after infection from forms of HIV isolated later in infection. These results could advance efforts to design vaccines and other prevention tools to block HIV in the early stages of sexual transmission, before infection takes hold.[3]

Advances in HIV Prevention Research

- **Treatment as prevention:** HIV Prevention Trials Network (HPTN) 052—In 2011, a large NIH-sponsored Phase III two-arm international multisite clinical trial showed that HIV-infected study participants who initiated ART immediately with CD4 counts of 350–550 cells/mm^3 were 96 percent less likely to transmit HIV to their uninfected partners than were those who delayed ART until their CD4 counts reached or fell below 250 cells/mm.[3] The vast majority of the couples (97 percent) were heterosexual. The study is continuing in order to assess the durability of the HIV prevention benefit. The journal *Science* selected HPTN 052 as the 2011 Breakthrough of the Year.[4]

[2] Kardava L, Moir S, Wang W, et al. Attenuation of HIV-associated human B cell exhaustion by siRNA downregulation of inhibitory receptors. *The Journal of Clinical Investigation*. 2011 Jul 1; 121(7):2614–24. Available at *http://www.jci.org/articles/view/45685*. doi:10.1172/jci45685.

[3] Nawaz F, Cicala C, Van Ryk D, et al. The genotype of early-transmitting HIV gp120s promotes α4β7 reactivity, revealing α4β7+/CD4+ T cells as key targets in mucosal transmission. *PLoS Pathogens*. 2011 Feb 24. Available at *http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1001301*.

[4] Available at *http://www.hptn.org/research_studies/hptn052.asp; http://www.nejm.org/doi/full/10.1056/NEJMoa1105243; http://www.sciencemag.org/content/334/6063/1628*.

- **Prevention of mother-to-child transmission (PMTCT):** Two recent studies have demonstrated the effectiveness of new multidrug ARV regimens for PMTCT during pregnancy and breastfeeding.[5] The Kesho Bora Study, co-funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and other organizations, determined that triple ARV prophylaxis for the mother during pregnancy and breastfeeding is safe and reduces the risk of HIV transmission to infants. Another study conducted in Botswana demonstrated that ART regimens from pregnancy through 6 months postpartum resulted in high rates of virologic suppression, with an overall rate of mother-to-child transmission of 1.1 percent.[6]
- **Pre-exposure prophylaxis (PrEP):** iPrEx, the Chemoprophylaxis for HIV Prevention in Men study, demonstrated that a daily tablet containing a combination of two ARV drugs used for HIV treatment can safely and effectively prevent HIV infection among men who have sex with men (MSM) and transgender women who have sex with men. Sponsored by NIAID, with additional funding from the Bill & Melinda Gates Foundation, the study found that uninfected study participants who took a daily dose of oral ARV drugs experienced an average of 43.8 percent fewer HIV infections than those who received a placebo pill. Higher rates of effectiveness up to 73 percent were found among study participants who adhered most closely to the daily drug regimen. Additional and continued research is needed to determine how to best use PrEP, and whether the approach will be similarly effective at preventing HIV infection in other at-risk populations.[7]
- **Microbicides:** For the first time in nearly 15 years of research, scientists discovered a vaginal microbicide gel that gives women a level of protection against HIV infection. The CAPRISA 004 study, conducted by the Centre for the AIDS Programme of Research in South Africa (CAPRISA) and sponsored by the U.S. Agency for International Development (USAID), found that the use of a microbicide gel containing a 1 percent concentration of the ARV drug tenofovir resulted in 39 percent fewer HIV infections compared with a placebo gel. The NIH provided substantial support and resources to establish the research infrastructure and training for CAPRISA. Ongoing and future clinical trials will build on these study results, with the goal of bringing a safe and effective microbicide to the general public.[8]
- **Behavioral research:** A National Institute on Drug Abuse (NIDA)-sponsored study successfully demonstrated a unique and innovative intervention aimed at reducing substance use and HIV health disparities among Hispanic youth. *Familias Unidas*, a Hispanic-specific, parent-centered program, is the only published behavioral intervention with demonstrated efficacy in preventing both substance use and unprotected sexual behavior among Hispanic youth. It is now being translated to community practice.[9]

APPROACHES TO HIV PREVENTION

- Vaccines
- Microbicides
- Behavior change/partner reduction
- Condoms, other barrier methods
- Treatment/prevention of drug/alcohol abuse
- Clean syringes
- Interruption of mother-to-child transmission
- Treatment of other sexually transmitted diseases
- Circumcision
- Pre-exposure prophylaxis (PrEP)
- Test and treat

[5] Kesho Bora study: Available at *http://www.ncbi.nlm.nih.gov/pubmed/21237718;* Botswana study: Available at *http://www.nejm.org/doi/full/10.1056/NEJMoa0907736.*

[6] Ibid.

[7] Grant RM, Lama JA, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine* 2010 Dec 30;363(27):2587–99. Epub 2010 Nov 23. Available at *http://www.ncbi.nlm.nih.gov/pubmed/21091279.*

[8] Karim QA, Karim SA, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science.* 2010 Sep 3;329(5996):1168–74. Epub 2010 July 19. Available at *http://www.sciencemag.org/content/329/5996/1168.full.* doi:10.1126/science.1193748.

[9] Information available at *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131683/?tool=pubmed.*

Advances in HIV Vaccine Research

- **RV 144, an HIV vaccine clinical trial:** Conducted in Thailand by the NIH and the Department of Defense, this study provided the first indication of a modest but positive effect in preventing HIV infection. The trial marked the first step in proving the concept that a vaccine to prevent HIV infection is feasible.[10] An extensive collaborative effort is underway to identify correlates of risk using blood samples from the RV144 study. These efforts already have yielded findings that may provide important direction for extending the efficacy of the candidate vaccine in that study, including the type of antibodies associated with reduced risk of HIV-1 infection.[11, 12, 13]
- **HIV-neutralizing antibodies:** Some HIV-infected individuals develop broadly neutralizing antibodies against HIV. Additional broadly neutralizing antibodies are rapidly being defined.[14, 15, 16, 17] To better understand how these antibodies develop, a collaborative research team led by investigators at the NIAID Vaccine Research Center (VRC) exploited structure-based and genomics approaches for dissecting common pathways of antibody binding and sequence maturation. These data are providing a roadmap of B-cell maturation necessary for generating broadly neutralizing antibodies, and may help to guide more effective design of protective AIDS vaccine immunogens.[18, 19]
- **Antibodies that help protect nonhuman primates from HIV-like virus:** Proof that newly defined, potent, broadly neutralizing monoclonal antibodies isolated from a subset of HIV-1 infected people could protect monkeys from an HIV-1-like virus was recently shown.[20, 21] In both studies, a combination of antibodies targeting different sites on the virus were delivered to chronically infected rhesus macaques, resulting in dramatically reduced viremia, suggesting that immunotherapy might help in treating infected people. If these neutralizing antibodies can be induced by vaccination, they should protect uninfected people as well.
- **Vaccine research in nonhuman primates:** Research in this area suggests that scientists are homing in on the critical components of a protective HIV vaccine and identifying new HIV vaccine candidates to test in human clinical trials. In the study, co-funded by NIAID, scientists report that several simian immunodeficiency virus (SIV) prime-boost vaccine regimens demonstrated partial protection against acquisition of infection by a virulent, tough-to-neutralize SIV strain that is different from the strain used to make the vaccine—a scenario analogous to what people might encounter if an HIV vaccine were available. The experimental vaccine regimens reduced the monkeys' likelihood of becoming infected per exposure to SIV by 80 to 83 percent compared with a placebo vaccine regimen. Further, in those monkeys that did become infected, the experimental vaccine regimens substantially reduced the amount of virus in the blood compared with controls.[22] The same group extended this approach to examine a global HIV-1 vaccine in

[10] Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *New England Journal of Medicine.* 2009 Dec 3; 361(23):2209–20. Available at *http://www.nejm.org/doi/full/10.1056/NEJMoa0908492*.

[11] Available at *http://www.hivvaccineenterprise.org/conference/2011/detailed-program*; *http://www.nejm.org/doi/full/10.1056/NEJMoa0908492*.

[12] Chung AW, Ghebremichael M, Robinson H, et al. Polyfunctional Fc-effector profiles mediated by IgG subclass selection distinguish RV144 and VAX003 vaccines. *Sci Transl Med.* 2014 Mar 19;6:228ra38. doi: 10.1126/scitranslmed.3007736.

[13] Yates NL, Liao HX, Fong Y, et al. Vaccine-induced Env V1-V2 IgG3 correlates with lower HIV-1 infection risk and declines soon after vaccination. *Sci Transl Med*. 2014 Mar 19;6:228ra39. doi:10.1126/scitranslmed.3007730.

[14] Scharf L, Scheid JF, Lee JH, et al. Antibody 8ANC195 reveals a site of broad vulnerability on the HIV-1 envelope spike. *Cell Rep.* 2014 May 8;7(3):785–795. doi: 10.1016/j.celrep.2014.04.001. Epub 2014 Apr 24.

[15] Blattner C, Lee JH, Sliepen K, et al. Structural delineation of a quaternary, cleavage-dependent epitope at the gp41-gp120 interface on intact HIV-1 Env trimers. *Immunity.* 2014 May 15;40(5):669–680. doi: 10.1016/j.immuni.2014.04.008. Epub 2014 Apr 24.

[16] Falkowska E, Le KM, Ramos A, et al. Broadly neutralizing HIV antibodies define a glycan-dependent epitope on the prefusion conformation of gp41 on cleaved envelope trimers. *Immunity.* 2014 May 15;40(5):657–668. doi: 10.1016/j.immuni.2014.04.009. Epub 2014 Apr 24.

[17] Sok D, Doores KJ, Briney B, et al. Promiscuous glycan site recognition by antibodies to the high-mannose patch of gp120 broadens neutralization of HIV. *Sci Transl Med*. 2014 May 14;6(236):236ra63. doi: 10.1126/scitranslmed.3008104.

[18] Wu X, Zhou T, Zhu J, et al. Focused evolution of HIV-1 neutralizing antibodies revealed by structures and deep sequencing. *Science*. 2011 Sept 16; 333(6049):1593–1602. Epub 2011 Aug 11. Available at *http://www.sciencemag.org/content/333/6049/1593*. doi:10.1126/science.1207532.

[19] Doria-Rose NA, Schramm CA, Gorman J, et al. Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies. *Nature.* 2014 May 1;509(7498):55–62. doi: 10.1038/nature13036. Epub 2014 Mar 2.

[20] Shingai M, Nishimura Y, Klein F, et al. Antibody-mediated immunotherapy of macaques chronically infected with SHIV suppresses viraemia. *Nature*. 2013 Nov 14;503(7475):277–80. doi: 10.1038/nature12746. Epub 2013 Oct 30.

[21] Barouch DH, Whitney JB, Moldt B, et al. Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys. *Nature.* 2013 Nov 14;503(7475):224–8. doi: 10.1038/nature12744. Epub 2013 Oct 30.

[22] Barouch DH, Liu J, Li H, et al. Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys. *Nature*. 2012 Feb 2; 482(7383):89–93. Epub 2012 Jan 4. Available at *http://www.nature.com/nature/journal/v482/n7383/full/nature10766.html*. doi:10.1038/nature10766.

rhesus macaques and confirmed vaccine-induced protection.[23] Plans are underway for early-stage clinical trials of a human-adapted version of one of the study's prime-boost vaccine combinations.

- **Research using novel vaccine vectors in nonhuman primates:** NIH-funded researchers showed that rhesus macaques could be protected from challenge with a highly pathogenic SIV using vaccine vectors based on rhesus cytomegalovirus to deliver SIV antigens. Despite being infected with the challenge virus, macaques that were vaccinated were able to control the infection for more than 1 year. Cell-associated SIV was only occasionally measurable at the limit of detection with ultrasensitive assays, observations that indicate the possibility of eventual viral clearance. Protection was shown to be associated with induction of effector memory CD8+ T cells, which were broadly reactive and immunologically atypical.[24, 25, 26] Studies are ongoing to determine the exact correlate of protection and to translate these findings in humans.

Advances in Prevention and Treatment of HIV-Associated Coinfections, Comorbidities, Malignancies, and Complications

- **Emerging cancer patterns in the chronically infected and aging HIV-infected population in the United States:** ART has dramatically prolonged the survival of HIV-infected patients, and the HIV-infected population in the United States is rapidly aging. In light of these trends, NIH researchers are documenting and directing research programs to address the challenges of an increase in the incidence of non-AIDS-defining cancers, such as lung cancer, anal cancer, and Hodgkin's lymphoma, in people living with HIV.[27]
- **Human papillomavirus (HPV) vaccine:** The incidence of anal cancer is rising very rapidly in the HIV-infected population. The HPV vaccine, GARDASIL®, which was developed in the National Cancer Institute (NCI) and licensed to Merck & Co. and to GlaxoSmithKline, has been shown to prevent anal intraepithelial neoplasia or anal cancer by preventing infection with oncogenic strains of HPV. In addition, this vaccine has been demonstrated to be safe and immunogenic in HIV-infected individuals.[28]
- **AIDS-related lymphoma:** The development of new regimens for the treatment of lymphoma and the tailoring of these regimens to specific tumor types has markedly improved the therapeutic outcome and survival of patients with AIDS-related lymphoma. In a recent NCI study, 95 percent of patients with germinal center B-cell lymphoma were progression-free at 5 years.[29]
- **HIV and tuberculosis (TB) coinfection:** TB accounts for half a million deaths worldwide every year for people living with AIDS. Findings from the Cambodia-based CAMELIA study, co-funded by NIAID and the French National Agency for Research on AIDS and Viral Hepatitis, demonstrated a 33 percent increase in survival in untreated, HIV-infected adults with very weak immune systems and newly diagnosed TB when they started ART 2 weeks after beginning TB treatment, rather than waiting 8 weeks, as had been standard.[30]
- **HIV-related neurological disorders:** Using an *in vitro* model of the blood-brain barrier, National Institute of Mental Health (NIMH)-supported researchers showed that even a small number of HIV-infected astrocytes were able to disrupt the barrier at specific sites. Migration of HIV across the

[23] Barouch DH, Stephenson KE, Borducchi EN, et al. Protective efficacy of a global HIV-1 mosaic vaccine against heterologous SHIV challenges in rhesus monkeys. *Cell*. 2013 Oct 24;155(3):531–9. doi: 10.1016/j.cell.2013.09.061. Epub 2013 Oct 24.

[24] Hansen SG, Ford JC, Lewis MS, et al. Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine. *Nature*. 2011 May 26; 473(7348):523–27. Epub 2011 May 11. Available at *http://www.nature.com/nature/journal/v473/n7348/full/nature10003.html*. doi:10.1038/nature10003.

[25] Hansen SG, Piatak M Jr, Ventura AB, et al. Immune clearance of highly pathogenic SIV infection. *Nature*. 2013 Oct 3;502(7469):100–4. doi: 10.1038/nature12519. Epub 2013 Sep 11.

[26] Hansen SG, Sacha JB, Hughes CM, et al. Cytomegalovirus vectors violate CD8+ T cell epitope recognition paradigms. *Science*. 2013 May 24;340(6135):1237874. doi: 10.1126/science.1237874.

[27] Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. *Journal of the National Cancer Institute*. 2011 May 4; 103(9):753–62. Epub 2011 Apr 11. Available at *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3086877*.

[28] Advisory Committee on Immunization Practices. Recommendations on the use of quadrivalent human papillomavirus vaccine in males. *Morbidity and Mortality Weekly Report*. 2011 Dec 23; 60(50):1705–08. Available at *http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6050a3.htm*.

[29] Dunleavy K, Little RF, Pittaluga S, et al. The role of tumor histogenesis, FDG-PET, and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-associated diffuse large B-cell lymphoma. *Blood*. 2010 Apr 15;115(15):3017–24. Epub 2010 Feb 3. Available at *http://www.ncbi.nlm.nih.gov/pubmed/20130244*. doi:10.1182/blood-2009-11-253039. Sparano JA, Lee JY, Kaplan LD, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. *Blood*. 2010 Apr 15;115(15):3008–16. Epub 2009 Dec 18. Available at *http://www.ncbi.nlm.nih.gov/pubmed/20023215*.

[30] Blanc F-X, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *New England Journal of Medicine*. 2011 Oct 20; 365(16):1471–81. Available at *http://www.ncbi.nlm.nih.gov/pubmed/22010913*.

blood–brain barrier is thought to be responsible for bringing virus into the brain and establishing chronic neuroinflammation affecting neurocognition and neurologic functioning.[31]

- **HIV-related dementia:** An NIMH-sponsored analysis of HIV-1 replication in the brain showed genetically distinct variants of HIV in the spinal fluid that may play a role in the development of HIV-associated dementia and related neurological disorders. This discovery is critical to understanding how these HIV-associated complications develop and how they can potentially be treated and prevented.[32] This may have implications for other viral diseases affecting the brain.

Advances in Improving HIV Testing and Detection

- **Mobile HIV testing and counseling services:** The large-scale NIMH-funded Project Accept trial conducted in South Africa, Tanzania, Zimbabwe, and Thailand determined that mobile, community-based voluntary HIV counseling and testing were four times more likely to identify individuals living with HIV infection than standard clinic-based HIV testing. The study investigators are currently determining if wide-scale mobile HIV testing and community mobilization activities can reduce HIV incidence.[33]
- **Rapid HIV testing strategy:** Findings from a recent NIDA-sponsored study demonstrated that nurse-initiated routine screening with rapid HIV testing and streamlined counseling in a primary care population resulted in increased rates of testing and receipt of test results, and was cost-effective compared with traditional HIV testing strategies. This study showed that rapid HIV testing can be successfully implemented in community treatment drug abuse centers and primary care settings, thus contributing to more comprehensive health care for specific high-risk populations.[34]

Advances in Preventing and Treating HIV in Children and Adolescents

- **Side effects of ARV drugs in children:** NICHD-funded and co-funded studies have demonstrated persistent, elevated cholesterol levels associated with ART in HIV-infected infants as well as in older children, and higher levels of biomarkers of vascular dysfunction than do HIV-exposed but uninfected children. The findings demonstrate that treatment of HIV-infected children with current anti-HIV therapies may place them at increased risk for cardiovascular diseases associated with high cholesterol that can develop later in life.[35] These findings can affect decisions regarding which treatment regimens to use in pediatric HIV patients and underscore the need for further research to develop new and better treatments with fewer side effects.
- **Language impairment in HIV-exposed, uninfected children:** Children exposed to HIV before birth but who are not infected are at risk for language impairment. NICHD-funded researchers found that in a group of school-age children born to HIV-infected women, 35 percent had difficulty understanding spoken words and expressing themselves verbally.[36]
- **Treatment for HIV-infected infants:** The NIAID-funded "Children with HIV Early Antiretroviral Therapy" (CHER) and PREDICT studies demonstrated the importance of identifying and treating HIV-infected infants as soon as possible to preserve the immune system and ensure healthy brain development.

[31] Eugenin EA, Clements JE, Zink MC, et al. Human immunodeficiency virus infection of human astrocytes disrupts blood-brain barrier integrity by a gap junction-dependent mechanism. *Journal of Neuroscience.* 2011 June 29; 31(26):9456–65. Available at *http://www.ncbi.nlm.nih.gov/pubmed/21715610.*

[32] Schnell G, Joseph S, Spudich S, et al. HIV-1 replication in the central nervous system occurs in two distinct cell types. *PLoS Pathogens.* 2011 Oct; 7(10). Epub 2011 Oct 6. Available at *http://www.ncbi.nlm.nih.gov/pubmed/22007152.*

[33] Sweat M, Morin S, Celentano D, et al. Community-based intervention to increase HIV testing and case detection in people aged 16–32 years in Tanzania, Zimbabwe, and Thailand (NIMH Project Accept, HPTN 043): A randomised study. *The Lancet Infectious Diseases.* 2011 Jul 1;11(7): 525–532 Epub 2011 May 4. Available at *http://globalhealth.med.ucla.edu/publications/lancetid.pdf.* doi:10.1016/s1473-3099(11)70060–3.

[34] Sanders GD, Anaya HD, Asch S, et al. Cost-effectiveness of strategies to improve HIV testing and receipt of results: Economic analysis of a randomized controlled trial. *Journal of General Internal Medicine.* 2010 Jun;25(6):556–63 Epub 2010 Mar 4. Available at *http://www.ncbi.nlm.nih.gov/pubmed/20204538.*

[35] Hazra R, Cohen RA, Gonin R, et al. Lipid levels in the second year of life among HIV-infected and HIV-exposed uninfected Latin American children. *AIDS.* 2012 Jan 14;26(2):235–40. Available at *http://www.ncbi.nlm.nih.gov/pubmed/22008654.*

[36] Rice ML, Buchanan AL, Siberry GK, et al. Language impairment in children perinatally infected with HIV compared to children who were HIV-exposed and uninfected. *Journal of Developmental & Behavioral Pediatrics.* 2012 Feb;33(2):112–23. Epub 2011 Dec 15. Available at *http://www.ncbi.nlm.nih.gov/pubmed/22179050.*

NIH AIDS Research Priorities

While these advances have the potential to make a significant impact on the pandemic, important scientific questions and challenges remain. Moving forward, the NIH is prioritizing the most critical and promising areas of research to address the continuing pandemic. The overarching priorities for research outlined in the *Trans-NIH Plan for HIV-Related Research* are:

- **Investing in basic research:** that will underpin further development of critically needed *vaccines and microbicides*.
- **Encouraging new investigators and new ideas:** including innovative multidisciplinary research and international collaborations to develop novel approaches to eliminate viral reservoirs and/or persistent and latent virus that could lead toward *a cure for HIV.*
- **Accelerating discovery through technology:** critical studies in the area of *therapeutics as a method to prevent infection,* including treatment to prevent HIV infection after exposure; PrEP; a potential prevention strategy known as "test and treat"; improved strategies to prevent mother-to-child transmission; and evaluation of prevention interventions that can be used in combination in different populations, including adolescents and older individuals.
- **Improving disease outcomes:** research focused on developing better, less toxic treatments; investigating how genetic determinants, sex, gender, race, age, nutritional status, treatment during pregnancy, and other factors interact to affect treatment success or failure and/or disease progression; studies addressing the increased incidence of malignancies, cardiovascular and metabolic complications, and premature aging associated with long-term HIV disease and ART.
- **Advancing translational sciences:** research on the feasibility, effectiveness, and sustainability required to scale up interventions from a structured behavioral or clinical study to a broader "real world" setting.

PRIORITY: Investing in Basic Research

The NIH will continue its strong commitment to basic scientific research, which is fundamental to its mission and essential to NIH efforts to enable innovation, address critical gaps, and capitalize on emerging scientific opportunities. Advances in basic science provide the building blocks to progress across all other scientific areas. Further research is needed to better understand the virus and how it causes disease, including studies to delineate how gender, sex, age, ethnicity, race, pregnancy, nutritional status, and other factors interact to influence vulnerability to infection and HIV disease progression and affect treatment success or failure. This includes research to better understand immune dysregulation and inflammation, and the development of HIV-associated comorbidities, malignancies, coinfections (including TB and hepatitis C), and cardiovascular, neurological, and other clinical complications. The NIH is increasing support for genetic studies and for research on eliminating viral reservoirs toward identifying a cure.

Etiology and Pathogenesis

The NIH supports a comprehensive portfolio of research focused on the transmission, acquisition, establishment, and maintenance of HIV infection and the causes and clinical complications of its associated immune deficiency. Research on basic HIV biology and AIDS pathogenesis has revolutionized the design of drugs, methodologies for diagnosis of HIV infection, and tools for monitoring disease progression and the safety and effectiveness of antiviral therapies.

The results from recent microbicide, vaccine, and PrEP clinical studies also have revealed gaps in knowledge and understanding of HIV etiology and pathogenesis, particularly with regard to host immune responses, how HIV interacts with and transverses mucosal surfaces, and the establishment and maintenance of latent viral reservoirs.

The NIH conducts and supports research on the biology of HIV transmission, which is essential for all HIV prevention research. This includes research to better understand HIV coinfections, comorbidities, and malignancies; factors related to premature aging and other complications; and research to better understand HIV

transmission, treatment, progression, and the unique clinical manifestations of HIV disease in women. Additional research examining the genetic determinants associated with HIV susceptibility, disease progression, and treatment response may lead to the development of customized therapeutic and preventive regimens formulated for an individual patient based on his or her genetic sequence.

Research examining the mechanisms by which HIV establishes and reactivates latent reservoirs of infection, and studies that further understanding of factors associated with the ability of the host to restrict HIV infection and/or mitigate HIV disease progression, also are high priorities for the NIH. A better understanding of these processes could help identify key targets for the development of new therapeutic strategies to prevent or control HIV infection or possibly lead to a cure for HIV infection and disease.

PRIORITY: Reducing New Infections

Prevention of new HIV infections is a key NIH research priority. Researchers are working to improve the many HIV prevention tools currently available, while adding new strategies to the toolbox. Reducing HIV incidence inevitably will require a combination of biomedical, behavioral, and structural interventions. Biomedical and behavioral interventions are urgently needed to reach individuals at risk, particularly in racial and ethnic populations in the United States, in international settings, among women, and among older individuals, adolescents, and MSM.

Vaccines

The best long-term hope for controlling the AIDS pandemic is the development of safe, effective, and affordable AIDS vaccines that may be used in combination with other prevention strategies. The NIH supports a broad AIDS vaccine research portfolio encompassing basic, preclinical, and clinical research, including studies to identify and better understand potentially protective immune responses in HIV-infected individuals and studies of improved animal models for the preclinical evaluation of vaccine candidates. Information gained from these studies is being used to inform the design and development of novel vaccine strategies. Since the announcement of the results of the RV144 trial in Thailand, the NIH has supported an unprecedented collaborative effort with investigators around the world to identify clues about the necessary immune responses required to protect against HIV acquisition.

Basic research studies on the virus and host immune responses, particularly those using samples from ongoing clinical trials, are critical to developing new and innovative vaccine concepts, as well as to the development of improved animal models to conduct preclinical evaluations of vaccine candidates.

ERADICATION OF VIRAL RESERVOIRS: TOWARD A CURE

NIH research in the field includes:

- **Pathogenesis studies:** Basic research on viral reservoirs, viral latency, and viral persistence. This includes studies on integration of HIV into the host genome, genetic factors associated with reactivation of the virus, and other barriers to HIV eradication.
- **Animal models:** Identification and testing of various animal and cellular models to mimic the establishment and maintenance of viral reservoirs. These studies are critical for testing novel or unique strategies for HIV reactivation and eradication.
- **Drug development and preclinical testing:** Programs to develop and preclinically test new and better ARV compounds capable of entering viral reservoirs, including the central nervous system.
- **Clinical trials:** Studies to evaluate lead compounds, drug regimens, and immune-based strategies capable of a sustained response to HIV. This includes clinical studies of drugs and novel approaches capable of eradicating HIV-infected cells and tissues.
- **Therapeutic vaccines:** Design and testing of vaccines that would be capable of suppressing viral replication and preventing disease progression.
- **Adherence/compliance:** Development and testing of strategies to maintain adherence/compliance to treatment, in order to improve treatment outcomes and reduce the risk of developing HIV drug resistance.

Microbicides

A safe and effective microbicide may be the best hope for woman-controlled HIV prevention. Microbicides are antimicrobial agents and other products that could be applied topically and used alone or in combination with other strategies to prevent transmission of HIV and other sexually transmitted infections. The NIH supports a comprehensive and innovative microbicide research program that includes the screening, discovery, development, preclinical testing, and clinical evaluation of microbicide candidates, including:

- Basic science research aimed at understanding how HIV crosses mucosal membranes and infects cells;
- Behavioral and social science research on adherence to and acceptability and use of microbicides among different populations;
- Studies of the safety of microbicide use during pregnancy and menopause;
- Studies in adolescents and in MSM;
- Implementation research to better understand how to integrate a potential product into community prevention practices; and
- Research on ethics, adherence, and other behavioral and social science issues that can affect clinical trials and product use.

Behavioral and Social Science

The NIH supports research to better understand the risk behaviors and social contexts that lead to HIV infection and disease progression, how to change those behavioral and social contexts, and how to maintain protective behaviors once they are adopted. NIH-supported research is developing and evaluating interventions targeted to substance abuse and sexual behaviors associated with HIV transmission, and studying the social and environmental factors associated with infection and disease outcomes, including housing, employment, health care access, stigma, and the role of interpersonal networks.

An important area of NIH research is determining effective strategies to test HIV-infected persons, link them to care, and promote adherence to ART. Studies have shown that early access to medical care improves outcomes and reduces direct medical treatment expenditures.

The NIH supports initiatives to better understand the multiple factors related to adherence, utilizing novel ways to ensure that patients take their medications and use prevention strategies appropriately. The NIH also supports research to improve recruitment and retention in clinical trials, to enhance statistical analysis of behaviors such as alcohol use that can affect clinical research.

Treatment as Prevention

A critical new area of prevention research is the study of treatment strategies as a method to prevent new HIV infections. This approach builds on NIH-sponsored landmark clinical trials that demonstrated that treatment of HIV-infected pregnant women could reduce transmission of HIV from mother to child significantly. Recent groundbreaking studies have demonstrated the successful use of ARVs to prevent transmission of HIV in specific populations.

Moving forward, the NIH is prioritizing efforts to expand basic, clinical, and applied knowledge about treatment as prevention through research to:

- Discover and test the next generation of ARV drugs that may be used in potential new PrEP strategies, particularly for women and adolescents;
- Improve the use of postexposure prophylaxis, the use of treatment to prevent HIV infection after accidental exposure, including in a health care environment;
- Improve PMTCT, including prevention of transmission through breast milk; and
- Evaluate a potential innovative prevention strategy known as "test and treat," to determine whether a community-wide HIV testing and counseling program with immediate treatment for HIV-infected individuals can decrease the overall rate of new HIV infections in that community.

NEW OPPORTUNITIES IN VACCINE RESEARCH

- Characterization of "transmitted/founder" HIV variants
- New immunologic assays for T cells and antibodies
- Genetic analysis of virus from infected vaccinees
- Development of alternative animal models
- New designs of vaccines ready for testing
- Advancement of HIV vaccine candidates to efficacy testing

PRIORITY:
Improving Disease Outcomes for HIV-Infected Individuals

Drug Discovery, Development, and Treatment

ART has improved immune function and delayed the progression of HIV disease in patients who are able to adhere to the treatment regimens and tolerate the toxicities and side effects associated with these drugs. At the same time, an increasing number of patients using ART are experiencing serious drug toxicities and developing drug resistance. Recent epidemiologic studies have shown that the incidence of coinfections, comorbidities, AIDS-defining and non-AIDS-defining malignancies, and complications associated with long-term HIV disease and ART are increasing. These include tuberculosis, hepatitis C, metabolic disorders, cardiovascular disease, conditions associated with aging, and neurologic and neurocognitive disorders.

The NIH supports a comprehensive therapeutics research program to design, develop, and test drugs and drug regimens. Priorities for development include drugs to maintain undetectable viral load; to overcome drug resistance and treatment failure; and to prevent and treat HIV-associated coinfections, comorbidities, and other complications. Research also is focused on the development of strategies that can eradicate persistent reservoirs of HIV infection.

Research Toward a Cure

An important new priority area for the NIH is research related to the potential for a cure or lifelong remission of HIV infection, including studies on viral persistence, latency, immune activation, and inflammation. A better understanding of these processes could lead to the development of therapies that eradicate persistent viral reservoirs, which might bring us to a possible cure for HIV infection and disease.

IMPROVED THERAPIES FOR LONG-TERM SURVIVAL

NIH researchers are working to:

- Develop innovative therapies and novel cell- and immune-based approaches to control and eradicate HIV infection
- Identify new drug targets based on the structure of HIV/host complexes
- Delineate the interaction of aging and AIDS, including neurological, cardiovascular, and metabolic complications, including issues of frailty
- Discover and develop improved therapies for AIDS-defining and non-AIDS-defining malignancies
- Discover the next generation of drugs that may be used in potential "therapeutics as prevention" strategies.

PRIORITY:
Reducing HIV-Related Disparities

The NIH is prioritizing research to better understand the causes of HIV-related health disparities, their role in disease transmission and acquisition, and their impact on treatment access and effectiveness. These include disparities among racial and ethnic populations in the United States, between developed and resource-constrained nations, between men and women, between youth and older individuals, and disparities based on sexual identity. As part of its efforts to help reduce these disparities, the NIH supports research training for new investigators from underrepresented populations, development of research infrastructure, and community outreach and information dissemination programs.

Training, Infrastructure, and Capacity Building

The NIH supports the training of domestic and international biomedical and behavioral AIDS researchers, and provides infrastructure, equipment, shared instrumentation, tissue and specimen repositories, and capacity-building support for the conduct of preclinical and clinical AIDS-related research.

In the United States, NIH-funded programs have increased the number of training positions for AIDS-related researchers, including programs designed to recruit individuals from underrepresented populations

into research careers and to build research infrastructure at minority-serving institutions. The NIH supports the NIH AIDS Research Loan Repayment Program and the Intramural AIDS Research Fellowship Program, which help ensure an adequate number of trained AIDS researchers at the NIH.

PRIORITY: Translating Research From Bench to Bedside to Community

NIH translational research addresses the feasibility, effectiveness, and sustainability required to scale up and implement interventions from a structured behavioral or clinical study to a broader "real world" setting. Related to this are critical epidemiologic and natural history studies, including the development of collaborative networks and specimen repositories. These studies evaluate various operational strategies to scale up and evaluate treatment programs and prevention interventions in communities at risk.

Natural History and Epidemiology

Natural history and epidemiologic research on HIV/AIDS in domestic and international settings is critical to monitoring the evolving pandemic, evaluating prevention modalities, characterizing the clinical manifestations of HIV disease and related comorbidities, and measuring the effects of treatment regimens at the population level.

The NIH supports a comprehensive research portfolio to study the epidemiologic characteristics of populations in which HIV is transmitted and the changing spectrum of HIV-related disease, including its coinfections, malignancies, and other complications. These studies have delineated the significant health disparities (e.g., racial and ethnic disparities in the United States, between industrialized and resource-constrained nations, between men and women, within younger and older age groups, and health disparities based on sexual identity) that are critical factors in the pandemic.

The NIH will continue to prioritize epidemiology studies of groups and populations affected by HIV and at high risk of infection, including individuals over 50 years of age, MSM, especially MSM of color, women, and adolescents. The NIH also will increase support for critical studies of the specific role of race and gender, the effects of increased HIV testing and linkage to care on HIV spread, the impact of therapy in changing the spectrum of HIV disease, and the preventable causes of death.

Information Dissemination

Effective information dissemination approaches are integral to HIV prevention and treatment efforts and critical in light of the continuing advent of new and complex ARV treatment regimens, issues related to adherence to prescribed treatments, and the need to translate behavioral and social science prevention approaches into practice. The changing pandemic and the increasing incidence of HIV infection in specific population groups in the United States, such as racial and ethnic populations, MSM, and women, underscore the need to disseminate HIV research findings and other related information to communities at risk. The flow of information among researchers, health care providers, and the affected communities represents new opportunities to rapidly translate research results into practice and to shape future research directions.

The NIH supports initiatives to enhance dissemination of research findings, develop and distribute state-of-the-art treatment guidelines, and enhance recruitment and retention of participants in clinical studies, including women, adolescents, and racial and ethnic populations. The NIH also prioritizes efforts to ensure that critical Federal guidelines on the use of ART and on the management of HIV complications for adults and children are updated regularly and disseminated to health care providers and patients through the *AIDSinfo* Web site *(http://www.aidsinfo.nih.gov)* and its Spanish language site *(http://infosida.nih.gov)*.